

World Journal of *Clinical Cases*

World J Clin Cases 2024 May 6; 12(13): 2138-2292



EDITORIAL

- 2138 Parenteral iron therapy in children with iron deficiency anemia
Roganovic J
- 2143 Treatment-induced neuroendocrine prostate cancer and *de novo* neuroendocrine prostate cancer: Identification, prognosis and survival, genetic and epigenetic factors
Wishahi M
- 2147 Perioperative cardiac risks in myasthenia gravis
Nag DS, Chatterjee A, Mahanty PR, Sam M, Bharadwaj MK
- 2151 Management of geriatric acetabular fractures: Contemporary treatment strategies
Tosounidis T, Chalidis B
- 2157 Pioneering role of machine learning in unveiling intensive care unit-acquired weakness
Dragonieri S

ORIGINAL ARTICLE**Case Control Study**

- 2160 Detection and analysis of serum bile acid profile in patients with colonic polyps
Ji X, Chen H
- 2173 Clinical analysis of colistin sulfate in the treatment of pneumonia caused by carbapenem-resistant Gram-negative bacteria
Xu HC, Cui Y, Wang XY, Wu HB, Li W, Wang D, Lin N, Lin L, Zhang YH

Retrospective Cohort Study

- 2182 Establishment and evaluation of a prognostic model for patients with unresectable gastric cancer liver metastases
Chang ZY, Gao WX, Zhang Y, Zhao W, Wu D, Chen L

Retrospective Study

- 2194 Therapeutic effect of Wendan Decoction combined with mosapride on gastroesophageal reflux disease after esophageal cancer surgery
Zhang YJ, Wu SP

Clinical Trials Study

- 2201 Yiwei Xiaoyu granules for treatment of chronic atrophic gastritis with deficiency syndrome of the spleen and stomach
Chen WQ, Fan QF, He YJ, Li F, Wu X, Li YP, Yang XJ

Observational Study

- 2210 Relationship between clinical belonging, professional identity, and nursing information ability among nursing interns: Model construction
Zhang G, Huang SJ, Li SF

META-ANALYSIS

- 2218 Efficacy and safety of Yangxinshi tablet for chronic heart failure: A systematic review and meta-analysis
Lu SH, Yu YF, Dai SS, Hu YQ, Liu JH

CASE REPORT

- 2231 Intra-thyroid esophageal duplication cyst: A case report
Lin HG, Liu M, Huang XY, Liu DS
- 2237 Magnetic resonance imaging findings of radiation-induced breast angiosarcoma: A case report
Wu WP, Lee CW
- 2243 Rim ¹⁸F-fluorodeoxyglucose uptake of hepatic cavernous hemangioma on positron emission tomography/computed tomography: A case report
Hu YA, Guo YX, Huang QF
- 2248 Recovering from prolonged cardiac arrest induced by electric shock: A case report
Zhang J, Qiao YR, Yang YD, Pan GZ, Lv CQ
- 2254 Young patient with a giant gastric bronchogenic cyst: A case report and review of literature
Lu XR, Jiao XG, Sun QH, Li BW, Zhu QS, Zhu GX, Qu JJ
- 2263 Airway management of a patient with linear immunoglobulin A bullous dermatosis: A case report
Nin OC, Hutnik R, Chheda NN, Hutchinson D
- 2269 Deferred revascularization in diabetic patient according to combined invasive functional and intravascular imaging data: A case report
Al Nooryani A, Aboushokka W, Beleslin B, Nedeljkovic-Beleslin B
- 2275 Thymic carcinoid with multiple bone metastases: A case report
Chen CQ, Huang MY, Pan M, Chen QQ, Wei FF, Huang H
- 2281 Atypical presentation of a posterior fossa tumour: A case report
Narotam A, Archary M, Naidoo P, Naidoo Y, Naidu V
- 2286 Refractory autoimmune hemolytic anemia in a patient with systemic lupus erythematosus and ulcerative colitis: A case report
Chen DX, Wu Y, Zhang SF, Yang XJ

ABOUT COVER

Peer Reviewer of *World Journal of Clinical Cases*, Konosuke Nakaji, FACP, MD, Doctor, Endoscopy Center, Aishinkai Nakae Hospital, Wakayama-shi 640-8461, Japan. parupurikopui@yahoo.co.jp

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Si Zhao*; Production Department Director: *Xiang Li*; Cover Editor: *Jim-Lei Wang*.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

May 6, 2024

COPYRIGHT

© 2024 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Case Control Study

Clinical analysis of colistin sulfate in the treatment of pneumonia caused by carbapenem-resistant Gram-negative bacteria

Hai-Chang Xu, Yan Cui, Xue-Ying Wang, Hai-Bo Wu, Wei Li, Dan Wang, Na Lin, Lin Lin, Ying-Hui Zhang

Specialty type: Medicine, research and experimental**Provenance and peer review:**

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind**Peer-review report's scientific quality classification**Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0**P-Reviewer:** Odhiambo A, Hungary**Received:** January 25, 2024**Peer-review started:** January 25, 2024**First decision:** February 8, 2024**Revised:** February 27, 2024**Accepted:** March 25, 2024**Article in press:** March 25, 2024**Published online:** May 6, 2024**Hai-Chang Xu, Yan Cui, Xue-Ying Wang, Hai-Bo Wu, Wei Li, Dan Wang, Na Lin, Lin Lin, Ying-Hui Zhang**, Department of Intensive Care Medicine, The General Hospital of the Northern Theater Command of the People's Liberation Army of China, Shenyang 110016, Liaoning Province, China**Corresponding author:** Yan Cui, MM, Deputy Director, Department of Intensive Care Medicine, The General Hospital of the Northern Theater Command of the People's Liberation Army of China, No. 83 Wenhua Road, Shenhe District, Shenyang 110003, Liaoning Province, China. cyan9010@qq.com

Abstract

BACKGROUND

Multidrug-resistant Gram-negative bacteria, exacerbated by excessive use of antimicrobials and immunosuppressants, are a major health threat.

AIM

To study the clinical efficacy and safety of colistin sulfate in the treatment of carbapenem-resistant Gram-negative bacilli-induced pneumonia, and to provide theoretical reference for clinical diagnosis and treatment.

METHODS

This retrospective analysis involved 54 patients with Gram-negative bacilli pneumonia admitted to intensive care unit of The General Hospital of the Northern Theater Command of the People's Liberation Army of China from August 2020 to June 2022. After bacteriological culture, the patients' airway secretions were collected to confirm the presence of Gram-negative bacilli. The patients were divided into the experimental and control groups according to the medication used. The research group consisted of 28 patients who received polymyxin sulfate combined with other drugs through intravenous, nebulization, or intravenous combined with nebulization, with a daily dosage of 1.5-3.0 million units. The control group consisted of 26 patients who received standard dosages of other antibiotics (including sulbactam sodium for injection, cefoperazone sodium sulbactam for injection, tigecycline, meropenem, or vaborbactam).

RESULTS

Of the 28 patients included in the research group, 26 patients showed improvement, treatment was ineffective for two patients, and one patient died, with the treatment efficacy rate of 92.82%. Of the 26 patients in the control group, 18

patients improved, treatment was ineffective for eight patients, and two patients died, with the treatment efficacy rate of 54.9%; significant difference was observed between the two groups ($P < 0.05$). The levels of white blood cell (WBC), procalcitonin (PCT), and C-reactive protein (CRP) in both groups were significantly lower after treatment than before treatment ($P < 0.05$), and the levels of WBC, PCT, and CRP in the research group were significantly lower than those in the control group ($P < 0.05$). Compared with before treatment, there were no significant changes in aspartate aminotransferase, creatinine, and glomerular filtration rate in both groups, while total bilirubin and alanine aminotransferase decreased after treatment ($P < 0.05$) with no difference between the groups. In patients with good clinical outcomes, the sequential organ failure assessment (SOFA) score was low when treated with inhaled polymyxin sulfate, and specific antibiotic treatment did not improve the outcome. Sepsis and septic shock as well as a low SOFA score were independent factors associated with good clinical outcomes.

CONCLUSION

Polymyxin sulfate has a significant effect on the treatment of patients with multiple drug-resistant Gram-negative bacilli pneumonia and other infections in the lungs and is safe and reliable. Moreover, the administration route of low-dose intravenous injection combined with nebulization shows better therapeutic effects and lower adverse reactions, providing new ideas for clinical administration.

Key Words: Colistin sulfate; Extensively drug-resistant; Pneumonia; Intravenous combined with nebulization; Sepsis; Nephrotoxicity; Neurotoxicity

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Multidrug-resistant Gram-negative bacteria, exacerbated by excessive use of antimicrobials and immunosuppressants, are a major health threat. Colistin sulfate provides comprehensive, highly sensitive coverage against these bacteria. For pulmonary infections, its use *via* intravenous and nebulization methods improves cure rates and reduces adverse reactions, including renal and neurotoxicity. It also significantly ameliorates clinical symptoms in sepsis patients, proving to be safe and reliable.

Citation: Xu HC, Cui Y, Wang XY, Wu HB, Li W, Wang D, Lin N, Lin L, Zhang YH. Clinical analysis of colistin sulfate in the treatment of pneumonia caused by carbapenem-resistant Gram-negative bacteria. *World J Clin Cases* 2024; 12(13): 2173-2181

URL: <https://www.wjgnet.com/2307-8960/full/v12/i13/2173.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v12.i13.2173>

INTRODUCTION

Polymyxin is a polypeptide antibiotic obtained from the culture solution of *Bacillus polymyxa*[1]. The components are named A, B, C, D, and E5 according to their chemical structures. Polymyxin B and Polymyxin E (sulfate polymyxin) were successfully developed in the 1950s and have been used in the treatment of infections caused by Gram-negative bacteria, particularly *Pseudomonas aeruginosa* (*P. aeruginosa*); however, they were abandoned in the 1970s owing to their narrow antibacterial spectrum and high nephrotoxicity[2]. With the extensive use of antimicrobial drugs and immunosuppressants, multidrug- or pandrug-resistant Gram-negative bacteria, particularly drug-resistant *Acinetobacter baumannii* (*A. baumannii*), *P. aeruginosa*, and *Klebsiella pneumoniae* (*K. pneumoniae*), pose a serious threat to human health. The number of drugs available for clinical use is decreasing, and the development and marketing of new antimicrobial drugs cannot keep pace with the rapidly increasing trend of drug resistance[3-4]. In recent years, the old drug polymyxin has achieved good results in infections caused by multidrug-resistant Gram-negative bacteria, including *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*, and has therefore received renewed clinical attention[5]. Polymyxin has multiple antibacterial mechanisms, mainly through acting on the bacterial cell membrane and causing important intracellular substances to leak, thus exhibiting bactericidal effect. In nature, many microbes exhibit drug resistance; therefore, finding a novel and highly effective broad-spectrum antibacterial agent has become a hot topic in the field of medicine. Polycationic polymyxin can bind to the outer membrane of Gram-negative bacteria, disrupt bacterial integrity, increase the permeability of the bacterial cell membrane, resulting in the leakage and death of major bacterial cell components[6]. Simultaneously, polymyxin carrying positive charge forms electrostatic bonds/interactions with negatively charged lipopolysaccharides on the bacterial cell membrane[7]. This electrostatic action can cause replacement of calcium and magnesium ions, which have a stabilizing effect on lipopolysaccharide molecules, in the outer membrane. This study observed that electrostatic action (1) has a great impact on the structure and function of polymyxin biofilm; (2) alters cell membrane permeability, reduces intracellular osmotic pressure, and inhibits phosphatidylinositol kinase activity; and (3) connects the polymyxin fatty acid chain more closely to the cell membrane, destroying bacterial cell integrity[8]. Second, an important characteristic of polymyxin is its ability to bind to lipopolysaccharides. It can inhibit the interaction between lipid and protein molecules through various pathways, thereby protecting the body from damage. In addition, it can

effectively prevent bleeding caused by damage to vascular endothelial cells. Notably, the lipid components of polymyxin can specifically bind to and remove lipopolysaccharides, which plays a crucial role in the treatment of endotoxin shock[9, 10]. Endotoxins are the major components in the outer membrane of Gram-negative bacteria and can activate macrophages and neutrophils to release inflammatory mediators and induce sepsis, causing tissue destruction or death[11-13]. Currently, specific anti-endotoxin drugs are lacking in clinical practice. Owing to its specific structure, polymyxin has been used as a lipopolysaccharide inactivator and adsorbent and clinically proven effective for the management of patients with sepsis[14]. Extensively drug-resistant *Gram-negative bacilli* (XDR-GNB) such as *Escherichia coli* (*E. coli*), *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii* are clinically important human pathogens[15]. The mortality rate of pneumonia caused by XDR-GN pathogens is extremely high. Currently, only a few effective antimicrobial strategies are available against XDR-GN bacteria[16]. Sulfate polymyxin has been used as a rescue therapy for pneumonia caused by XDR-GNB[4]. In addition, emerging cephalosporin-class beta-lactamase inhibitors (ceftazidime-avibactam, cefepime-tazobactam, ceftolozane, and eravacycline) are active against XDR-GNB that cause pneumonia in intensive care unit (ICU) patients. In addition to sulfate polymyxin, new cephalosporins can be used to treat pneumonia caused by XDR-GNB[17]. However, owing to the high cost of new cephalosporin/beta-lactamase inhibitors, unavailability in middle-income countries, high antibiotic pressure in the ICU, and high risk of antibiotic resistance, polymyxin is considered the best treatment for pneumonia caused by XDR-GNB. Researchers have found that intravenous injection leads to poor distribution of sulfate polymyxin at the infection site, which may have a negative impact on the treatment of pneumonia and tracheobronchitis caused by multidrug-resistant XDR-GNB. Inhalation therapy has shown a wide prospect of expanding indications, including respiratory diseases such as lower respiratory tract infections[18]. Theoretically, the inhalation route of administration is more appropriate for sulfate polymyxins to directly reach at the infection site and reduce systemic side effects[19]. Polymyxin sulfate is the first antibiotic independently developed by China, which is fermented by *Bacillus polymyxa*. Its main components are polymyxin E1 (also known as colistin A) and polymyxin E2 (also known as polymyxin B). It is an active drug that does not require hydrolysis in the body to exert antibacterial activity. Studies have found that as an important choice for combined or single treatment of intravenous antimicrobial drugs, the adjunctive nebulization route can improve the clinical effect and microbial eradication rate of patients with XDR-GNB pneumonia, and its safety is relatively high. However, it does not affect the overall mortality rate of patients with hospital-acquired pneumonia/ventilator-associated pneumonia[20-23].

MATERIALS AND METHODS

Subjects

This is a retrospective study involving 105 patients with pneumonia caused by XDR-GN who were admitted to the ICU of The General Hospital of the Northern Theater Command of the People's Liberation Army of China between August 2020 and June 2022. Since it is a retrospective study, the informed consent is waived. The inclusion criteria were as follows: Age 18–80 years; confirmed diagnosis of pneumonia caused by XDR *E. coli*, *K. pneumoniae*, *P. aeruginosa*, or *A. baumannii*; at least two consecutive samples on different d (minimum time interval of 24 h) showing the presence of XDR-GNB in bronchial secretions or bronchoalveolar lavage samples; and at least six doses of inhaled or intravenous sulfate polymyxin. Patients under 18 years or over 80 years of age, with polymicrobial pneumonia, cystic fibrosis, or lung transplantation were excluded.

Relevant diagnostic criteria

Antimicrobial susceptibility testing was performed *in vitro*, following the norms used in the clinical and laboratory standard studies. Resistance was evaluated based on the minimum inhibitory concentration (MIC), which is widely recognized for guiding rational drug use. Currently, MIC is one of the most commonly used international indicators for evaluating the efficacy and safety of antimicrobial drugs. XDR-GNB are defined as a class of bacteria that are only relatively sensitive to polymyxin, and mainly include *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*, as detected in the laboratory[24].

Clinical outcomes were divided into three stages: Clinical cure (symptoms and signs related to the infection disappeared after the administration of sulfate polymyxin), clinical improvement (improved when compared with before the administration of sulfate polymyxin), and clinical failure (continued or worsened symptoms and signs related to the infection even after the administration of sulfate polymyxin and/or death). Infection recurrence was defined as the appearance of symptoms, such as fever and shortness of breath, within 72 h after stopping sulfate polymyxin; laboratory indicators indicating bacterial infection, such as CRP, procalcitonin (PCT), and white blood cell (WBC) count; and no other infection foci. Favorable clinical outcomes include clinical cure or improvement, and unfavorable outcomes include clinical failure or recurrence[25]. Two physicians who were unaware of the study protocol independently analyzed the clinical outcomes. None of the participants underwent any examination or trial. There were no significant differences between the groups. In case of a discrepancy with the clinical outcome in patients, the reviewer will re-evaluate the information.

Treatment methods

The study involved 54 patients who were divided into experimental and control groups according to their medication status. In the research group, 28 patients were treated with sulfate polymyxin (National Medicine Approval Number H31020822, batch number 20180324) in combination with tigecycline at a daily dosage of 150–300 million units, administered intravenously, nebulized, or a combination of both. The efficacy and adverse reactions were observed in the

two groups. The control group of 26 patients received the standard dosage of another antibiotic (tigecycline). To avoid serious side effects caused by inhaled polymyxin B, inhaled glucocorticoids and bronchodilators were administered 30 min before treatment. A vibrating mesh nebulizer was used to improve the nebulization performance of inhaled sulfate polymyxin. The vibrating mesh nebulizer is placed upstream of the inspiratory arm and a constant inspiratory flow volume control method is selected. The humidification system is removed during inhalation, and it is restored after nebulization. All patients receive the same nebulized dose of drug treatment: 125000 to 250000 units *per use*. Lung function was reviewed every two wk or one month. After nebulization, the expiratory filter was replaced. Each treatment group was implemented by one or two experienced physicians. Both treatment groups received the same treatment measures at each stage. All subjects were randomly divided into two groups for controlled trials. In both treatment groups, sulfate polymyxin was administered for more than 3 d.

Clinical efficacy evaluation

Referring to the "Technical Guiding Principles for Clinical Trials of Antimicrobial Drugs"[26], clinical efficacy of different treatments was analyzed in all patients. This includes general condition, clinical features, and non-microbiological indicators, including biochemical indicators and laboratory examinations. The clinical effectiveness in all patients was evaluated based on the WBC count, PCT level, and CRP level before and after the treatment. The SOFA scoring system was used to score the patients.

Liver and kidney function evaluation

The changes in the liver and kidney function indicators, such as total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and glomerular filtration rate, were recorded and analyzed. Microbiological diagnoses were performed using routine biochemical methods.

Neurotoxicity reaction diagnostic criteria[27]

Grade 0: No clinical manifestations; Grade 1: Sensory dullness, completely disappeared within one wk; Grade 2: Completely disappeared within 21 d; Grade 3: Did not completely disappear within 21 d; Grade 4: Accompanied by functional impairment.

Statistical analysis

Statistical analyses were performed using SPSS 22.0. Continuous data were expressed as mean \pm SD, and independent sample *t*-test was used for comparison between groups; discrete data were expressed as percentages, and chi-square test (χ^2 test) was used for comparison between groups. $P < 0.05$ indicated that the difference was statistically significant. The study explores the clinical effectiveness of sulfate polymyxin and its impact on in-hospital mortality: With or without sepsis; *A. baumannii* drug-resistant bacteria and *E. coli* drug-resistant bacteria and *P. aeruginosa* XDR bacteria; with or without immunosuppression as indicators; the median SOFA score was used to assess patients' conditions.

RESULTS

General patient information

A total of 54 patients diagnosed with pneumonia caused by XDR-GN bacteria, who were admitted to our hospital between August 2020 and June 2022, were included in the study. The clinical data mainly included the following aspects: The research group was comprised of 15 males and 13 females of age ranging from 24 to 75 years, with an average of (57.22 \pm 11.07) years. The control group was comprised of 14 males and 12 females of age ranging from 28 to 78 years, *i.e.*, (57.22 \pm 11.07) years. All patients had confirmed diagnosis of pneumonia caused by XDR-GN bacteria based on sputum culture and bacteriological examination. There was no statistically significant difference between the two groups, and all research subjects were diagnosed with pulmonary infectious diseases according to the standards of the National Institutes of Health in the United States. The hospitalized patients were randomly divided into experimental and control groups. The research group comprising 28 patients was administered polymyxin sulfate in combination with anti-infective therapy, of which 8 were administered intravenous medication, 10 were administered nebulized medication, and 10 were administered a combination of intravenous and nebulized medications. The duration of polymyxin sulfate medication was 3–55 (10.94 \pm 1.86) d. The control group of 26 patients was treated with tigecycline in combination with anti-infective therapy, of which 6 were administered intravenous medication, 10 were administered nebulized medication, and 10 were administered a combination of intravenous and nebulized medications. The duration of antibiotic medication was 3–55 (11.43 \pm 4.98) d.

Clinical efficacy

The research group included 28 patients, of which 26 patients showed clinical improvement, one patient showed clinical failure of the treatment, and another one patient died. The treatment efficacy rate was 92.82%. The control group included 26 patients, of which 18 showed clinical improvement, six patients showed clinical failure, and two patients died. The treatment efficacy rate was 69.23%. There was a significant difference in the treatment efficacy rate between the two groups ($P < 0.05$).

Comparison of laboratory test results before and after treatment in both groups

The comparison of laboratory test results before and after treatment in the two groups showed that the levels of WBC, PCT, and CRP significantly decreased after treatment compared with before treatment in both groups, and the difference was statistically significant ($P < 0.05$), as shown in Table 1. The levels of WBC and PCT significantly decreased after treatment in the research group, and CRP level significantly decreased in both groups.

Comparison of liver and kidney functions before and after treatment in both groups

There were no significant changes in AST, creatinine, and glomerular filtration rate before and after treatment in both groups, but total bilirubin and ALT levels decreased to varying degrees in control group ($P < 0.05$, Table 2). There were no significant differences in other indicators between the two groups.

Comparison of neurotoxicity before and after treatment in both groups

The incidence of neurotoxicity was as follows: Grade 0, 19 cases (67.85%); Grade 1, five cases (17.85%); Grade 2, three cases (10.71%); and Grade 3, one case (3.57%), with a total incidence of nine cases (32.14%) in the research group *vs* 15 (57.69%), 5 (19.23%), 5 (19.23%), 1 (3.84%), and 11 (42.30%), respectively, in the control group. There were no significant differences between the two groups ($\chi^2 = 3.02$, $P > 0.05$), as shown in Table 1.

Comparison of clinical features after treatment between the two groups

Univariate analysis of clinical features of 54 patients with pneumonia showed that patients treated with inhaled polymyxin sulfate had good clinical outcomes and lower SOFA scores (Table 3).

DISCUSSION

A. baumannii, *K. pneumoniae*, and *P. aeruginosa* are the most common Gram-negative bacilli causing pneumonia[28]. Pathogens present in ICU show antibiotic resistance[29]. The mortality rate of pneumonia caused by XDR-GNB is high (46%–60%)[30]. Because polymyxin sulfate has poor permeability through the lung parenchyma and causes systemic toxicity when administered intravenously, nebulized polymyxin sulfate is often used to treat pneumonia caused by multidrug-resistant or Gram-negative bacilli[31]. However, the lack of optimization of nebulization technology and dosage limitations restrict its clinical application[32]. Existing clinical and experimental evidence suggest that nebulized high-dose colistimethate sodium may be effective against multidrug resistance. Whether nebulized high-dose polymyxin sulfate is therapeutically equivalent or better compared to intravenous ceftazidime (cephalosporin)/ β -lactamase (lactamase) inhibitor is not yet known. Nebulized polymyxin sulfate is also used to treat pneumonia caused by multidrug-resistant bacilli. However, there have been few reports on its safety when used to treat respiratory infections. This article reviews the results of the related clinical trials and discusses these issues. Previous studies have shown that the clearance rate of *K. pneumoniae* infection when treated with intravenous and nebulized polymyxin sulfate is higher than that with polymyxin sulfate alone. The combined use of intravenous injection and nebulization can also reduce the average intubation time and amount of polymyxin sulfate used during ICU hospitalization[33]. The main side effects of polymyxin include nephrotoxicity and neurotoxicity[34]. Polymyxin exhibits certain degree of damaging effect on various systems of the human body. The most common clinically used are β -lactam antibiotics (such as ampicillin). Polymyxin can enter various organs of the body through the blood; the most significant toxicity of polymyxin is renal toxicity. Most drug-induced nephrotoxicity is caused by at least one pathogenic mechanism, including changes in glomerular hemodynamics, tubular cell toxicity, inflammation, oxidative damage, crystal nephropathy, or thrombotic microangiopathy[35]. Renal tubular epithelial cells are the main target cells of polymyxin. The accumulation of high concentrations of polymyxin in the renal tubules causes severe apoptosis and necrosis of the epithelial cells[36]. Polymyxin binds to glycoproteins on the apical cell membrane, resulting in increased cell membrane permeability, excretion of cations, anions, and cell fluids, and continuous cell damage[37]; at the same time, some *in vitro* animal experiments have also proven that the nephrotoxicity caused by polymyxin can increase reactive oxygen species due to the inhibition or damage of the body's existing antioxidant defense system by the drug, thereby causing tissue cell oxidative damage and renal function damage[38].

The incidence of neurotoxicity associated with polymyxin sulfate in the past 20 years has not been high, and the condition is mild, with no severe symptoms, of muscle relaxation and respiratory paralysis. However, damage to the central nervous system, particularly acute cerebral ischemic attack, has attracted widespread attention. This article reviews the neurotoxic effects of polymyxin sulfate and the underlying mechanisms. The reason of neurotoxicity may be that the neurons are rich in lipids, and polymyxin sulfate can combine with cell membrane lipids. Polymyxin sulfate binds to the presynaptic binding site at the neuromuscular junction, inhibiting the release of acetylcholine into the synapse, thus causing adverse reactions[39]. Similar to nephrotoxicity, polymyxin-induced neurotoxicity is concentration dependent. It mainly manifests as motor and sensory function disorders, ataxia, and motor neuron injury. Severe neurotoxicity can cause epileptic seizures, coma, and death. Serious complications often cause patients to become disabled for life, and thus needs critical consideration. Because the incidence of neurotoxicity is low and the onset is relatively mild, no specific treatment is provided in clinical practice, and symptoms can disappear by reducing the dose or stopping the medication.

Sepsis, septic shock, and high SOFA scores could significantly affect the results. The differences between the current research and previous trial results may be due to different doses and study populations. This review describes different

Table 1 Comparison of white blood cell, procalcitonin, C-reactive protein levels in both group patients

Group	White blood cell ($\times 10^9/L$)	Procalcitonin ($\mu g/L$)	C-reactive protein (mg/L)
Control Group ($n = 26$)			
Before treatment	8.72 \pm 2.36	2.58 \pm 1.23	59.62 \pm 25.03
After treatment	8.53 \pm 1.52 ^a	3.86 \pm 0.22 ^a	39.42 \pm 12.87 ^a
Treatment Group ($n = 28$)			
Before treatment	10.42 \pm 2.87	2.22 \pm 0.67	57.66 \pm 22.46
After treatment	6.25 \pm 2.72 ^{a,b}	0.54 \pm 0.11 ^{a,b}	29.54 \pm 13.43 ^{a,b}

^a $P < 0.05$, compared with before treatment.

^b $P < 0.05$, compared with after treatment of control group.

Table 2 Comparison of total bilirubin, alanine transaminase, aspartate aminotransferase, creatinine, and glomerular filtration rate in both groups

Group	TBIL ($\mu mol/L$)	ALT (U/L)	AST (U/L)	Cr ($\mu mol/L$)	GFR (mL/min)
Control group ($n = 26$)					
Before treatment	43.4 \pm 20.97 ^a	42.35 \pm 4.55 ^a	40.29 \pm 9.16	78.54 \pm 15.67	97.28 \pm 23.06
After treatment	23.43 \pm 5.28	35.96 \pm 3.66	39.88 \pm 8.54	85.46 \pm 12.67	102.87 \pm 30.24
Treatment group ($n = 28$)					
Before treatment	38.92 \pm 5.04	46.75 \pm 7.43	43.11 \pm 7.28	77.89 \pm 15.38	92.45 \pm 20.33
After treatment	38.26 \pm 9.16	41.13 \pm 8.75	42.54 \pm 10.01	72.34 \pm 16.43	98.29 \pm 18.98

^a $P < 0.05$, compared with before treatment.

TBIL: Total bilirubin; ALT: Alanine transaminase; AST: Aspartate aminotransferase; Cr: Creatinine; GFR: Glomerular filtration rate.

Table 3 Logistic regression analysis of predictive factors related to good clinical outcomes in 105 pneumonia

Variable	OR	95%CI	P value
Sulfate colistin treatment	2.93	1.03-5.88	0.027
SOFA score	0.88	0.79-0.96	0.005
Septic shock	0.42	0.17-0.88	0.021

SOFA: Sequential organ failure assessment; OR: Odds ratio.

clinical situations and proposes suggestions for improving the efficacy. Intravenous administration is the most commonly used route for administering medication to patients with sepsis and other infections. Existing research suggests that the amount of polymyxin B used for intravenous and non-intravenous administration is relatively small, and that there are many types of pathogens.

Polymyxin class of drugs (MDR) show strong antibacterial activity against *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and other Gram-negative bacteria and have become the "last line of defense" for the treatment of MDR Gram-negative bacteria in foreign clinics. However, its pharmacokinetics, pharmacodynamics, and toxicology are not yet fully understood; therefore, there are certain limitations on its clinical application. This article reviews the progress made by domestic and foreign scholars in the pharmacokinetics and other aspects of polymyxin class of drugs in recent years. Optimization of the medication plan; selection of the best dosage, method of administration, and interval of medication; and improvement in the efficacy and safety of medication warrant a large number of randomized controlled trials.

CONCLUSION

This study shows that compared to the conventional intravenous administration of polymyxin sulfate, nebulized administration of polymyxin sulfate along with intravenous administration does not provide better efficacy and bactericidal effect in patients with pneumonia caused by Gram-negative bacilli in the clinical setting. However, by controlling continuous bacterial contamination of the respiratory tract from tracheal intubation (reduction of inoculum), it may provide more beneficial clinical results. Although there are no such issues with non-specific infections, such as bronchitis and emphysema, intravenous injection of polymyxin sulfate combined with nebulization may also be used for other diseases. The study suggests a novel administration approach for clinical application and helps develop feasible treatment plans that are safer and more acceptable to patients.

FOOTNOTES

Author contributions: Xu HC and Cui Y conceptualized the research project, wrote the paper and checked for scientific accuracy; Wang XY and Wu HB collected data and checked the manuscript for scientific accuracy; Li W and Wang D collected data, performed statistical analyses and checked the manuscript for scientific accuracy; Lin N, Lin L and Zhang YH collected data, performed statistical analyses and checked the manuscript for scientific accuracy.

Institutional review board statement: The study was approved by the Ethics Committee of the People's Liberation Army Northern Theater General Hospital (No: Y2024-016).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: There are no conflicts of interest for any of the authors of this study.

Data sharing statement: All the authors report no relevant conflicts of interest for this article.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and revised according to the STROBE Statement – checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Hai-Chang Xu 0009-0009-4504-0106; Yan Cui 0009-0007-7871-4854.

S-Editor: Liu H

L-Editor: A

P-Editor: Zhao S

REFERENCES

- Chen Y, Mu XL. [Clinical Retrospective Study on the Treatment of ICU Patients with Pulmonary Acinetobacter Baumannii Infection by Polymyxin E]. *Kongjun Yike Daxue Xuebao* 2022; 7: 871-874, 878
- Cai CL, Wang T, Tang C, Qian WD. [Study on the Resistance of Escherichia Coli Mutated by Low Energy Nitrogen Ion Implantation to Polymyxin B]. *Xian Gongye Daxue Xuebao* 2022; 42: 217-222
- Wang MJ, Xu JQ, Song WF, Liu XL. [The Effect of Polymyxin B on Autophagy of Rat Hepatic Stellate Cells Induced by Lipopolysaccharide]. *Zhongguo Yiyao Kexue* 2022; 12: 35-38
- Deng T. [Study on the Role of Rhodomycin in Restoring the Sensitivity of Drug-resistant Gram-negative Bacteria to Polymyxin and Tigecycline]. M.Sc. Thesis, Yangzhou University, 2022 [DOI: [10.27441/d.cnki.gyzdu.2022.002404](https://doi.org/10.27441/d.cnki.gyzdu.2022.002404)]
- Bian MY, Zhang Q. [Clinical Analysis of Polymyxin B Sulfate in the Treatment of Hospital-acquired Pneumonia Caused by Multidrug-resistant Gram-negative Bacteria]. *Shiyong Yaowu Yu Linchunag* 2022; 25: 243-246
- Miguela-Villoldo P, Moreno MA, Rodríguez-Lázaro D, Gallardo A, Hernández M, Serrano T, Sáez JL, de Frutos C, Agüero M, Quesada A, Domínguez L, Ugarte-Ruiz M. Longitudinal study of the mcr-1 gene prevalence in Spanish food-producing pigs from 1998 to 2021 and its relationship with the use of polymyxins. *Porcine Health Manag* 2022; 8: 12 [PMID: [35300732](https://pubmed.ncbi.nlm.nih.gov/35300732/) DOI: [10.1186/s40813-022-00255-0](https://doi.org/10.1186/s40813-022-00255-0)]
- de Carvalho FRT, Telles JP, Tuon FFB, Rabello Filho R, Caruso P, Correa TD. Antimicrobial Stewardship Programs: A Review of Strategies to Avoid Polymyxins and Carbapenems Misuse in Low Middle-Income Countries. *Antibiotics (Basel)* 2022; 11 [PMID: [35326841](https://pubmed.ncbi.nlm.nih.gov/35326841/) DOI: [10.3390/antibiotics11030378](https://doi.org/10.3390/antibiotics11030378)]
- Ramaloko WT, Osei Sekyere J. Phylogenomics, epigenomics, virulome and mobilome of Gram-negative bacteria co-resistant to carbapenems and polymyxins: a One Health systematic review and meta-analyses. *Environ Microbiol* 2022; 24: 1518-1542 [PMID: [35129271](https://pubmed.ncbi.nlm.nih.gov/35129271/) DOI: [10.1111/1462-2920.15930](https://doi.org/10.1111/1462-2920.15930)]

- 9 **Martin-Loeches I**, Leone M, Einav S. Antibiotic Stewardship: Dead Bugs do not Mutate. *J Transl Int Med* 2022; **10**: 290-293 [PMID: 36860631 DOI: 10.2478/jtim-2022-0059]
- 10 **Silva KED**, Rossato L, Leite AF, Simionato S. Overview of polymyxin resistance in Enterobacteriaceae. *Rev Soc Bras Med Trop* 2022; **55**: e0349 [PMID: 35239902 DOI: 10.1590/0037-8682-0349-2021]
- 11 **Han CL**, Wei HX. [Clinical Efficacy Analysis of Tigecycline Combined with Polymyxin in the Treatment of Patients with Pulmonary Infection Caused by Multidrug-resistant Bacteria]. *Zhongguo Zhiye Yaoshi* 2021; **18**: 90-94
- 12 **Queiroz PA**, Meneguello JE, Silva BR, Caleffi-Ferracioli KR, Scodro RB, Cardoso RF, Marchiosi R, Siqueira VL. Proteomic profiling of *Klebsiella pneumoniae* carbapenemase (KPC)-producer *Klebsiella pneumoniae* after induced polymyxin resistance. *Future Microbiol* 2021; **16**: 1195-1207 [PMID: 34590903 DOI: 10.2217/fmb-2021-0005]
- 13 **Rodríguez-Santiago J**, Cornejo-Juárez P, Silva-Sánchez J, Garza-Ramos U. Polymyxin resistance in Enterobacterales: overview and epidemiology in the Americas. *Int J Antimicrob Agents* 2021; **58**: 106426 [PMID: 34419579 DOI: 10.1016/j.ijantimicag.2021.106426]
- 14 **Zhang FS**, Ma FY. [Clinical Study on the Treatment of Ventilator-associated Pneumonia Infected by *Acinetobacter Baumannii* with Polymyxin B Sulfate and Sulbactam Sodium]. *Zhongguo Xiandai Yaowu Yingyong* 2021; **15**: 124-127 [DOI: 10.14164/j.cnki.cn11-5581/r.2021.13.045]
- 15 **Li YJ**, Wang HT, Ma XP, Teng W, Zhou JJ. [Efficacy Observation of Polymyxin B Combined with Cefoperazone Sodium Sulbactam Sodium and Tigecycline in the Treatment of Multidrug-resistant *Acinetobacter Baumannii* Pneumonia]. *Zhongwen Keji Ziliao Mulu (Zhongcaoyao Fence)* 2021; **44**: 376-380
- 16 **Zhang X**, Qu F, Jia W, Huang B, Shan B, Yu H, Tang Y, Chen L, Du H. Polymyxin resistance in carbapenem-resistant Enterobacteriaceae isolates from patients without polymyxin exposure: a multicentre study in China. *Int J Antimicrob Agents* 2021; **57**: 106262 [PMID: 33347990 DOI: 10.1016/j.ijantimicag.2020.106262]
- 17 **Wu Y**, Zhang J. Standardized inhalation capability assessment: A key to optimal inhaler selection for inhalation therapy. *J Transl Int Med* 2023; **11**: 26-29 [PMID: 37223614 DOI: 10.2478/jtim-2022-0073]
- 18 **Periasamy H**, Gnanamani A. Polymyxins resistance among Gram-negative pathogens in India. *Lancet Infect Dis* 2020; **20**: 1362-1363 [PMID: 33186513 DOI: 10.1016/S1473-3099(20)30855-0]
- 19 **Perez LRR**, Carniel E, Narvaez GA, Dias CG. Evaluation of a polymyxin drop test for polymyxin resistance detection among non-fermentative gram-negative rods and enterobacterales resistant to carbapenems. *APMIS* 2021; **129**: 138-142 [PMID: 33164263 DOI: 10.1111/apm.13096]
- 20 **Dhaouadi S**, Soufi L, Hamza A, Fedida D, Zied C, Awadhi E, Mtibaa M, Hassen B, Cherif A, Torres C, Abbassi MS, Landolsi RB. Co-occurrence of mcr-1 mediated colistin resistance and β -lactamase-encoding genes in multidrug-resistant *Escherichia coli* from broiler chickens with colibacillosis in Tunisia. *J Glob Antimicrob Resist* 2020; **22**: 538-545 [PMID: 32251867 DOI: 10.1016/j.jgar.2020.03.017]
- 21 **Zhang K**, Liang JP, Zhong XZ. [Efficacy and Safety of Polymyxin B in the Treatment of Ventilator-associated Pneumonia Caused by Multidrug-resistant Bacteria]. *Yixue Daobao* 2020; **38**: 432-435 [DOI: 10.3870/j.issn.1004-0781.2020.01.00222]
- 22 **Sartori L**, Sellera FP, Moura Q, Cardoso B, Fontana H, Côrtes LA, Cerdeira L, Lincopan N. Genomic features of a polymyxin-resistant *Klebsiella pneumoniae* ST491 isolate co-harboring bla (CTX-M-8) and qnrE1 genes from a hospitalised cat in São Paulo, Brazil. *J Glob Antimicrob Resist* 2020; **21**: 186-187 [PMID: 32224265 DOI: 10.1016/j.jgar.2020.03.006]
- 23 **Shoib M**, Hussain A, Satti L, Hussain W, Zaman G, Hanif F. Evaluation of rapid polymyxin Nordmann Poirel test for detection of polymyxin resistance in clinical isolates of Enterobacteriaceae. *Eur J Clin Microbiol Infect Dis* 2020; **39**: 2195-2198 [PMID: 32529457 DOI: 10.1007/s10096-020-03942-4]
- 24 **Doi Y**, van Duin D. Polymyxin Resistance in *Klebsiella pneumoniae*: Complexity at Every Level. *Clin Infect Dis* 2020; **70**: 2092-2094 [PMID: 31513703 DOI: 10.1093/cid/ciz627]
- 25 **Liu AM**. [Clinical Distribution and Drug Sensitivity Analysis of 96 Strains of Multidrug-resistant *Acinetobacter Baumannii*]. *Zhongxiyi Jiehe Huli* 2020; **7**: 172-174
- 26 **Xu YH**, Zhang SH, Liu H. [Study on the In vitro Antibacterial Activity of Polymyxin B Combined with Drugs Against Carbapenem-resistant *Klebsiella pneumoniae* Pneumonia]. *Zhongguo Xiaoduxue Zazhi* 2020; **37**: 260-262 [DOI: 10.11726/j.issn.1001-7658.2020.04.007]
- 27 **Wang WL**, Ding WQ, Huang JD, Chen LX, Yu F. [Observation of the Effect of Meropenem Combined with Polymyxin B Sulfate on Patients with Pan-drug-resistant *Acinetobacter Baumannii* Bacteremia and its Impact on PCT and CRP]. *Quanke Yixue Linchuang Yu Jiaoyu* 2020; **18**: 212-214 [DOI: 10.13558/j.cnki.issn1672-3686.2020.003.006]
- 28 **Filioussis G**, Kachrimanidou M, Christodoulou G, Kyritsi M, Hadjichristodoulou C, Adamopoulou M, Tzivara A, Kritas SK, Grinberg A. Short communication: Bovine mastitis caused by a multidrug-resistant, mcr-1-positive (colistin-resistant), extended-spectrum β -lactamase-producing *Escherichia coli* clone on a Greek dairy farm. *J Dairy Sci* 2020; **103**: 852-857 [PMID: 31733863 DOI: 10.3168/jds.2019-17320]
- 29 **Hassen B**, Abbassi MS, Ruiz-Ripa L, Mama OM, Hassen A, Torres C, Hammami S. High prevalence of mcr-1 encoding colistin resistance and first identification of bla (CTX-M-55) in ESBL/CMY-2-producing *Escherichia coli* isolated from chicken faeces and retail meat in Tunisia. *Int J Food Microbiol* 2020; **318**: 108478 [PMID: 31855787 DOI: 10.1016/j.ijfoodmicro.2019.108478]
- 30 **Huang C**, Xiao YH. [Clinical Application and Dilemma of Polymyxin]. *Yixue Daobao* 2020; **39**: 10-16 [DOI: 10.3870/j.issn.1004-0781.2020.01.002]
- 31 **Huang M**, Lv QP, Hu SS. [Analysis of the Distribution and Drug Resistance of Major Pathogens in the Comprehensive ICU]. *Zhihui Jiankang* 2019; **5**: 30-32 [DOI: 10.19335/j.cnki.2096-1219.2019.36.015]
- 32 **Gazel D**, Tatman Otkun M, Akçali A. In vitro activity of methylene blue and eosin methylene blue agar on colistin-resistant *a. baumannii*: an experimental study. *J Med Microbiol* 2019; **68**: 1607-1613 [PMID: 31535963 DOI: 10.1099/jmm.0.001078]
- 33 **Boluki E**, Moradi M, Azar PS, Fekrazad R, Pourhajbagher M, Bahador A. The effect of antimicrobial photodynamic therapy against virulence genes expression in colistin-resistance *Acinetobacter baumannii*. *Laser Ther* 2019; **28**: 27-33 [PMID: 31190695 DOI: 10.5978/islsm.28_19-OR-03]
- 34 **Moon SH**, Kaufmann Y, Huang E. Paenipeptin Analogues Potentiate Clarithromycin and Rifampin against mcr-1-Mediated Polymyxin-Resistant *Escherichia coli* In Vivo. *Antimicrob Agents Chemother* 2020; **64** [PMID: 32015033 DOI: 10.1128/AAC.02045-19]
- 35 **Moffatt JH**, Harper M, Boyce JD. Mechanisms of Polymyxin Resistance. *Adv Exp Med Biol* 2019; **1145**: 55-71 [PMID: 31364071 DOI: 10.1007/978-3-030-16373-0_5]
- 36 **Scott A**, Pottenger S, Timofte D, Moore M, Wright L, Kukavica-Ibrulj I, Jeukens J, Levesque RC, Freschi L, Pinchbeck GL, Schmidt VM, McEwan N, Radford AD, Fothergill JL. Reservoirs of resistance: polymyxin resistance in veterinary-associated companion animal isolates of *Pseudomonas aeruginosa*. *Vet Rec* 2019; **185**: 206 [PMID: 31239295 DOI: 10.1136/vr.105075]

- 37 **Sobur A**, Haque ZF, Sabuj AA, Ievy S, Rahman AT, El Zowalaty ME, Rahman T. Molecular detection of multidrug and colistin-resistant *Escherichia coli* isolated from house flies in various environmental settings. *Future Microbiol* 2019; **14**: 847-858 [PMID: 31373221 DOI: 10.2217/fmb-2019-0053]
- 38 **Zhao CY**, Wang YD, Li XY, Ma LY, Yang ST. [Clinical Characteristics and Prevention and Control Measures of Carbapenem-resistant Enterobacteriaceae]. *Zhongguo Chuanranbing Zazhi* 2019; **37**: 321-326 [DOI: 10.3760/cma.j.issn.1000-6680.2019.06.001]
- 39 **Qian MR**. [New Progress in the Study of the Mechanism of Action of Polymyxin B]. *Gansu Yixue* 2019; **38**: 397-399



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

